DuPont SHE Excellence Center
1007 Market Street
Wilmington, DE 19898

DUPONT

DuPont SHE Excellence Center

October 11, 2000

Carol Browner, Administrator
U.S. Environmental Protection Agency
Attn: Chemical Right-to-Know Program
P.O. Box 1473
Merrifield, VA 22116

Dear Ms. Browner:

E. I. du Pont de Nemours and Company (DuPont) is committed to participation in the High Production Volume (HPV) Challenge Program. One of our sponsorship commitments was for the chemical Dimethyl ether (DME), CAS No. 115-10-6. As part of our sponsorship, we are enclosing the robust data summary and test plan for this chemical. You will note that the basic testing is complete for DME and no further testing is proposed for this chemical. Please contact me (302-773-0910, edwin.l.mongan-1@usa.dupont.com) if you have comments or questions regarding this submission.

Sincerely,

Edwin L. Mongan III
Manager, Environmental Stewardship

/ELM
Enclosure

CC: Charles Auer – U. S. EPA

11-October-2000

ROBUST SUMMARY FOR DIMETHYL ETHER

Summary

Dimethyl ether (DME) is highly water-soluble, has a melting point of -141.5°C and boils at -24.8°C. DME is a colorless gas at room temperature with an ethereal odor, a vapor pressure of 4450 mm Hg @ 25°C and is highly flammable in air (3.4-18%).

When released to air, DME exists as a vapor at ambient temperatures. Degradation of DME in air occurs by reaction with hydroxyl and nitrate radicals with estimated half-lives of 5.4 and 123 days, respectively. Direct photolysis is not expected to be an important degradation process. If released into rivers or lakes, DME is expected to volatilize with estimated half-lives of 2.1 hours and 2.7 days, respectively. Lacking a hydrolyzable functional group, DME is not expected to undergo hydrolysis in the environment. DME exhibits low toxicity to fish and aquatic invertebrates with a low bioconcentration potential in aquatic organisms.

DME exhibits low acute toxicity by the inhalation route with a 4-hour LC_{50} in rats of 164,000 ppm (16.4% DME in air). In beagle dogs, DME has been shown to produce cardiac sensitization following inhalation of ≥ 200,000 ppm DME (20% DME) but not at 100,000 ppm DME (10% DME). In a lifetime inhalation study in rats, DME produced slight hemolytic (blood) effects at 25,000 ppm (2.5% DME) and was negative for carcinogenicity. The no-observable-adverse-effect-level (NOAEL) for this life-time inhalation study was 2000 ppm (0.2% DME) and was based on an increase in body weight and decrease in survival in male rats exposed at 10,000 and 25,000 ppm, and on the blood effects seen at the 25,000 ppm exposure level. In developmental studies, pregnant rats exposed by inhalation to atmospheres containing 4% DME (40,000 ppm) over the gestation days of 6-15 exhibited mild anesthetic effects; the fetal NOAEL was 0.125% DME (1250 ppm) based on an increased incidence of skeletal variations at the 0.5% DME dose level. However, DME was not teratogenic at concentrations up to 4% DME (40,000 ppm). Also, following exposure to DME in air for 2 years, no reproductive toxicity was noted at inhalation dose levels up to 2.5% DME (25,000 ppm). DME is non-mutagenic and non-clastogenic when tested *in vitro*. It was also negative in the *in vivo* sex-linked recessive lethal assay with *Drosophila melanogaster*.

In humans, exposure to DME occurs principally by the inhalation route. Under controlled laboratory exposures of up to 100,000 ppm (10% DME) mild yet reversible CNS effects were noted. Human exposure to atmospheres containing greater than 144,000 ppm (14.4% DME) resulted in unconsciousness after approximately 26 minutes.

The current exposure standards, for both the American Industrial Hygiene Association (AIHA) 8-hour TWA and the German MAK, which are based on the NOAEL in rats following life-time exposure to 2000 ppm (0.2% DME), has been set at 1000 ppm, or 0.1% DME for an 8-hour daily life-time exposure. Acute exposures to DME from

consumer goods where DME is used as a propellant have been shown to be in the range of 100 ppm for short (<15 minutes/day) periods daily, well below levels known to produce CNS effects.

TEST PLAN FOR DIMETHYL ETHER

Dimethyl Ether CAS No. 115-10-6	**Data Available**	**Data Acceptable**	**Testing Required**
Study	**Y/N**	**Y/N**	**Y/N**
Physical/Chemical Characteristics			
Melting Point	Y	Y	N
Boiling Point	Y	Y	N
Vapor Pressure	Y	Y	N
Partition Coefficient	Y	Y	N
Water Solubility	Y	Y	N
ENVIRONMENTAL FATE			
Photodegradation	Y	Y	N
Stability in Water	Y	Y	N
Transport (Fugacity)	Y	Y	N
Biodegradation	Y	Y	N
ECOTOXICITY			
Acute Toxicity to Fish	Y	Y	N
Acute Toxicity to Invertebrates	Y	Y	N
Acute Toxicity to Aquatic Plants	Y	Y	N
MAMMALIAN TOXICITY			
Acute Toxicity	Y	Y	N
Repeated Dose Toxicity	Y	Y	N
Developmental Toxicity	Y	Y	N
Reproductive Toxicity	Y	Y	N
Genetic Toxicity Gene Mutations	Y	Y	N
Genetic Toxicity Chromosomal Aberrations	Y	Y	N

The studies listed below were selected to represent the best available study design and execution for these HPV toxicity endpoints. Other data of equal or lesser quality are not summarized, but are listed as additional references in this document.

1.0 Substance Information

CAS Number:	115-10-6
Chemical Name:	Methane, oxybis-
Structural Formula:	CH_3-O-CH_3
Other Names:	Demeon D Dimethyl ether Dimethyl oxide DME Dymel® A Methoxymethane Methyl ether Wood ether
Exposure Limits:	1000 ppm, 8- and 12-hour TWA: DuPont Acceptable Exposure Limit (AEL) 1000 ppm (1880 mg/m^3), 8-hour TWA: AIHA WEEL 1000 mL/m^3 Limit value; TWA = 1000 ppm or 1910 mg/m^3: MAC (NL) 1000 mL/m^3 Limit value; Short-term limit value = 2000 mL/m^3 for 60 minutes, three times per shift, skin notation: MAC (DE)

2.0 Physical/Chemical Properties

2.1 Melting Point

Value:	-141.5°C
Decomposition:	No Data
Sublimation:	No Data
Method:	No Data
GLP:	Unknown
Reference:	Lide, D. R. (ed.) (1995-1996). CRC Handbook of Chemistry and Physics, 76th ed., p. 3-207, CRC Press Inc., Boca Raton, FL.
Reliability:	Not assignable because limited study information was

available.

Additional References for Melting Point:

Grasselli, J. G. and W. M. Ritchey (1975). Chemical Rubber Company Atlas of Spectral Data and Physical Constants for Organic Compounds, 2nd ed., CRC Press Inc., Cleveland, Ohio (ISHOW/305968).

Riddick, J. A. et al. (1986). Techniques of Chemistry, 4th ed., p. 1325, Wiley Interscience, New York (ENVIROFATE/111214).

Weast, R. C. (1989). Handbook of Chem. & Physics, 69th ed.

Compressed Gas Association (1966). Handbook of Compressed Gases, Reinhold Publishing Corp., New York (cited in IUCLID (1995). IUCLID Data Sheet "dimethyl ether" (October 23)).

2.2 Boiling Point

Value:	-24.8°C
Decomposition:	No Data
Pressure:	No Data
Method:	No Data
GLP:	Unknown
Reference:	Lide, D. R. (ed.) (1995-1996). CRC Handbook of Chemistry and Physics, 76th ed., p. 3-207, CRC Press Inc., Boca Raton, FL.
Reliability:	Not assignable because limited study information was available.

Additional References for Boiling Point:

DuPont Co. (1999). Material Safety Data Sheet No. CEFD000A (March 24).

Grasselli, J. G. and W. M. Ritchey (1975). Chemical Rubber Company Atlas of Spectral Data and Physical Constants for Organic Compounds, 2nd ed., CRC Press Inc., Cleveland, Ohio (ISHOW/305960).

Kennedy et al. (1941). JACS 63, 2267 (cited in IUCLID (1995). IUCLID Data Sheet "dimethyl ether" (October 23)).

Riddick, J. A. et al. (1986). Techniques of Chemistry, 4th ed., p. 1325, Wiley Interscience, New York (ENVIROFATE/111215).

2.3 Density

Value:	1.91855 g/L @ 1 atm and 25°C
Temperature:	No Data
Method:	No Data
GLP:	Unknown
Results:	No additional data.
Reference:	Budavari, S. (ed.). (1996). The Merck Index – An Encyclopedia of Chemicals, Drugs, and Biologicals, p. 1037, Merck and Co., Inc., Whitehouse Station, NJ.
Reliability:	Not assignable because limited study information was available.

Additional References for Density:

DuPont Co. (1999). Material Safety Data Sheet No. CEFD000A (March 24).

IUCLID (1995). IUCLID Data Sheet "dimethyl ether" (October 23).

2.4 Vapor Pressure

Value:	4450 mm Hg @ 25°C
Temperature:	No Data
Decomposition:	No Data
Method:	No Data
GLP:	Unknown
Reference:	Riddick, J. A. et al. (1985). Techniques of Chemistry, 4th ed., Volume II. Organic Solvents, p. 1325, John Wiley and Sons, New York, NY.
Reliability:	Not assignable because limited study information was available.

Additional References for Vapor Pressure:

Daly, J. J., Jr. and G. L. Kennedy, Jr. (1987). Chem. Times Trends, 10(1):40-44, 54.

DuPont Co. (1999). Material Safety Data Sheet No. CEFD000A (March 24).

Jordan, E. T. (1954). Vapor Pressure of Organic Compounds, Inter-Science Publishers, Inc., New York (ISHOW/305970).

Cardosa, E. and A. Bruno (1923). J. Chim. Physiq., 20:347 (cited in IUCLID (1995). IUCLID Data Sheet "dimethyl ether" (October 23)).

2.5 Partition Coefficient (log Kow)

Value:	0.10
Temperature:	No Data
Method:	No Data
GLP:	Unknown
Reference:	Hansch, C. et al. (1995). Exploring QSAR – Hydrophobic, Electronic, and Steric Constants, p. 5, American Chemical Society, Washington, DC.
Reliability:	Not assignable because limited study information was available.

Additional References for Partition Coefficient (log Kow):

Leo, A. J. (1978). Report of the Calculation of Octanol/Water Log P Values for Structures in EPA Files (ISHOW/305973).

IUCLID (1995). IUCLID Data Sheet “dimethyl ether” (October 23).

SRC (Syracuse Research Corporation) (1988). Calculated values using CLOGP3-PCGESM (ENVIROFATE/111220).

2.6 Water Solubility

Value:	35.3 g/L
Temperature:	25°C
pH/Pka:	No Data
Method:	No Data
GLP:	Unknown
Reference:	Riddick, J. A. et al. (1985). Techniques of Chemistry, 4th ed., Volume II, Organic Solvents, p. 1325, John Wiley and Sons, New York, NY.
Reliability:	Not assignable because limited study information was available.

Additional References for Water Solubility:

Budavari, S. (ed.). (1996). The Merck Index – An Encyclopedia of Chemicals, Drugs, and Biologicals, p. 1037, Merck and Co., Inc., Whitehouse Station, NJ (HSDB/354).

Daly, J. J. Jr. and G. L. Kennedy, Jr. (1987). Chem. Times Trends, 10(1):40-44, 54.

DuPont Co. (1989). Material Safety Data Sheet No. 2006FR (November 14).

DuPont Co. (1999). Material Safety Data Sheet No. CEFD000A (March 24).

Perry, J. H. (1950). Chemical Engineers Handbook, McGraw-Hill Book Co. Inc., New York (ISHOW/305971).

RWE Gesellschaft fur Forschung und Entwicklung (1991). Unpublished Report, Wesseling (cited in IUCLID (1995). IUCLID Data Sheet "dimethyl ether" (October 23)).

RWE Gesellschaft fur Forschung und Entwicklung (1993). Report, Wesseling (cited in IUCLID (1995). IUCLID Data Sheet "dimethyl ether" (October 23)).

2.7 Flash Point

Value:	-42°F (-5.5°C)
Method:	Closed cup
GLP:	Unknown
Reference:	Lewis, R. J. (1996). Sax's Dangerous Properties of Industrial Materials, 9th ed., Volumes 1-3, p. 2237, Van Nostrand Reinhold, New York, NY.
Reliability:	Not assignable because limited study information was available.

Additional References for Flash Point:

DuPont Co. (1999). Material Safety Data Sheet No. CEFD000A (March 24).

RWE Gesellschaft fur Forschung und Entwicklung (1994). Wesselring (cited in IUCLID (1995). IUCLID Data Sheet "dimethyl ether" (October 23)).

2.8 Flammability

Results:	3.4%-18%
Method:	By volume in air
GLP:	Unknown
Reference:	DuPont Co. (1999). Material Safety Data Sheet No. CEFD000A (March 24).
Reliability:	Not assignable because limited study information was available.

Additional References for Flammability:

Kirwin, C. J. and J. B. Galvin (1993). Patty's Industrial Hygiene and Toxicology, 4th ed., Vol IIA, p. 445-525.

Lewis, R. J. (1996). Sax's Dangerous Properties of Industrial Materials, 9th ed.,

Vol. 1-3, p. 2237, Van Nostrand Reinhold, New York (HSDB/354).

National Fire Protection Guide (1991). Fire Protection Guide on Hazardous Materials, 10th ed., p. 49-74, National Fire Protection Association, Quincy, MA (HSDB/354).

National Materials Advisory Board (1882). Report of the Committee on Evaluation of Industrial Hazards, National Research Council Publication NMAB 353-5, National Academy Press, Washington, DC (cited in IUCLID (1995). IUCLID Data Sheet "dimethyl ether" (October 23)).

3.0 Environmental Fate

3.1 Photodegradation

Concentration:	Not Applicable
Temperature:	No Data
Direct Photolysis:	Not Applicable
Indirect Photolysis:	Not Applicable
Breakdown Products:	Not Applicable
Method:	The rate constant for the vapor-phase reaction of dimethyl ether with photochemically-produced hydroxyl radicals was 2.98×10^{-12} cm^3/molecule-sec at 25°C (Atkinson, 1994). This rate constant corresponds to an atmospheric half-life of about 5.4 days at an atmospheric concentration of 5×10^5 hydroxyl radicals per cm^3 (SRC, n.d.). Direct photolysis is not expected to be an important removal process since aliphatic ethers do not absorb light in the environmental spectrum (Calvert and Pitts, 1966). The rate constant for the reaction of dimethyl ether with hydroxyl radicals in aqueous solution is 1.0×10^9 L/mol sec (Buxton et al., 1988). This rate constant corresponds to a half-life of about 2.2 years (SRC, n.d.) at an average aqueous hydroxyl radical concentration of 1×10^{-17} mol/L (Mill et al., 1980). The rate constant for the reaction of dimethyl ether with nitrate radicals is 2.6×10^{-16} cm^3/molecule-sec at 22°C (Langer and Ljungstroem, 1994). This corresponds to an atmospheric half-life of about 123 days at an average atmospheric concentration of 5×10^8 nitrate radicals per cm^3 (Atkinson, 1991; SRC, n.d.). Dimethyl ether is not expected to undergo hydrolysis in the environment due to the lack of hydrolyzable functional groups (Lyman et al., 1990).
GLP:	Not Applicable

Reference: Atkinson R. (1994). J. Phys. Chem. Ref. Data, Monograph 2, p. 132 (HSDB/354).

Calvert, J. G. and J. N. Pitts Jr. (1966). Photochemistry, pp. 441-2, John Wiley and Sons, New York, NY (HSDB/354).

Buxton, G. V. et al. (1988). J. Phys. Chem. Ref. Data, 17:513-882 (HSDB/354).

Mill, T. et al. (1980). Science, 207:886-7 (HSDB/354).

Langer, S. and E. Ljungstroem (1994). Comm. Eur. Communities, Eur 1994, (15609, Physico-chemical behaviour of atmospheric pollutants Vol 1) pp. 114-7 (HSDB/354).

Atkinson, R. (1991). J. Phys. Chem. Ref. Data, 20:459-507 (HSDB/354).

Lyman, W. J. et al. (1990). Handbook of Chemical Property Estimation Methods, pp. 7-4, 7-5, Amer. Chem. Soc., Washington, DC (HSDB/354).

SRC (Syracuse Research Corporation) (n.d.). (HSDB/354).

Reliability: Estimated value based on accepted model.

Additional Reference for Photodegradation:

Data from this additional source support the study results summarized above. This study was not chosen for detailed summarization because the data were not substantially additive to the database.

IUCLID (1995). Calculated from D. Rhasa and R. Zellner (1987). Free. Rad. Res. Comms., 3(1-5):199-209 and Atkinson, R. (1986). Chem. Rev., 69-201.

3.2 Stability in Water

Concentration: Not Applicable
Half-life: Not Applicable
% Hydrolized: Not Applicable
Method: The Henry's Law constant for dimethyl ether is estimated as 7.6×10^{-3} atm-m^3/mole (SRC, n.d.) from its vapor pressure, 4450 mm Hg, and water solubility, 3.53×10^4 mg/L (Riddick et al., 1986). This Henry's Law constant indicates that dimethyl ether is expected to volatilize rapidly from water

	surfaces (Lyman et al., 1990; SRC, n.d.). Based on this Henry's Law constant, the estimated volatilization half-life from a model river (1 m deep, flowing 1 m/sec, wind velocity of 3 m/sec) is approximately 2.1 hours (Lyman et al., 1990; SRC, n.d.). The estimated volatilization half-life from a model lake (1 m deep, flowing 0.05 m/sec, wind velocity of 0.5 m/sec) is approximately 2.7 days (Lyman et al., 1990; SRC, n.d.). Dimethyl ether's Henry's Law constant (Riddick et al., 1986; SRC, n.d.) indicates that volatilization from moist soil surfaces may occur (SRC, n.d.). Volatilization of dimethyl ether from dry soil surfaces is expected (SRC, n.d.) based upon this compound's vapor pressure (Riddick et al., 1986).
GLP:	Not Applicable
Reference:	Riddick, J. A. et al. (1986). Organic Solvents: Physical Properties and Methods of Purification. Techniques of Chemistry, 4th ed., Wiley-Interscience, New York, NY (HSDB/354). Lyman, W. J. et al. (1990). Handbook of Chemical Property Estimation Methods, pp. 15-1 to 15-29, Amer. Chem. Soc., Washington, DC (HSDB/354). SRC (Syracuse Research Corporation) (n.d.). (HSDB/354).
Reliability:	Estimated value based on accepted model.

Additional Reference for Stability in Water:

Data from this additional source support the study results summarized above. This study was not chosen for detailed summarization because the data were not substantially additive to the database.

RWE Gesellschaft fur Forschung und Entwicklung, Wesselring (1993). Report (cited in IUCLID (1995). IUCLID Data Sheet "dimethyl ether" (October 23)).

3.3 Transport (Fugacity):

Media:	Air, Water, Soil, Sediments	
Distributions:	Air:	98.2%
	Water:	1.67%
	Soil:	0.108%
	Sediment:	0.003%
Adsorption Coefficient:	Not Applicable	
Desorption:	Not Applicable	
Volatility:	Not Applicable	

Method:	Calculated according to Mackay, Level III, Syracuse Research Center Epiwin Version 3.05 Data Used: Molecular Weight: 46.07 Henry's Law Constant: 0.00131 atm-m^3/mole (Henry database) Vapor Pressure: 3.85x10^3 (Mpbpwin program) Log Kow : 0.1 (Kowwin program) Soil Koc : 1.29 (Pckocwin program)
GLP:	No
Reference:	Syracuse Research Corporation EPIWIN v3.05 contains a Level III fugacity model. The methodology and programming approach was developed by Dr. Donald Mackay and co-workers which is detailed in: Mackay, D. (1991). Multimedia Environmental Models; The Fugacity Approach, pp 67-183, Lewis Publishers, CRC Press. Mackay, D. et al. (1996). Environ. Toxicol. Chem., 15(9):1618-1626. Mackay, D. et al. (1996). Environ. Toxicol. Chem., 15(9): 1627-1637.
Reliability:	Estimated value based on accepted model.

Additional References for Transport (Fugacity): None Found.

3.4 Biodegradation

Value:	In an aerobic test, 2 mg/L of DME was 5% degraded after 28 days. Methane-utilizing microorganisms, abundantly present in nature, play a significant role in the removal of DME from aquatic ecosystems and soils.
Breakdown Products:	No Data
Method:	Directive 84/449/EEC, C.4 "Biotic degradation – modified AFNOR test NF T90/302". The inoculum used was activated sludge, domestic.
GLP:	Test was under GLP working conditions, but not yet certified.
Reference:	Akzo sponsored study, October 1989 (cited in IUCLID (1995). IUCLID Data Sheet "dimethyl ether" (October 23)). Sterling, D. I. and H. Dalton (1979). FMS Microbiol. Lett., 5:315-318 (cited in IUCLID (1995). IUCLID Data Sheet

	"dimethyl ether" (October 23)).
	Sterling, D. I. And H. Dalton (1980). J. Gen. Microbiol., 116:277-283 (cited in IUCLID (1995). IUCLID Data Sheet "dimethyl ether" (October 23)).
	Colby, J. et al. (1977). Biochem. J., 165:394-402 (cited in IUCLID (1995). IUCLID Data Sheet "dimethyl ether" (October 23)).
	Patel, R. N. et al. (1982). Appl. Environ. Microbio., 44(5):1130-1137 (cited in IUCLID (1995). IUCLID Data Sheet "dimethyl ether" (October 23)).
	Patel, R. N. et al. (1978). J. Bacteriol., 136:352-348 (cited in IUCLID (1995). IUCLID Data Sheet "dimethyl ether" (October 23)).
	Hazeu, W. (1975). Antonie van Leeuwenhoek, 41:121-134 (cited in IUCLID (1995). IUCLID Data Sheet "dimethyl ether" (October 23)).
Reliability:	Not assignable because limited study information was available.

Additional Reference for Biodegradation:

Data from this additional source support the study results summarized above. This study was not chosen for detailed summarization because the data were not substantially additive to the database.

Chemicals Inspection and Testing Institute (1992). Japan Chemical Industry Ecology – Toxicology and Information Center, ISBN 4-89074-101-1 2-49 (HSDB/354).

3.5 Bioconcentration

Value:	BCF 0.70 (SRC, n.d.).
Method:	The estimated value was calculated using a log Kow of 0.10 (Hansch et al., 1995) and a regression-derived equation (Lyman et al., 1990). According to a classification scheme (Franke et al., 1994), this BCF suggests the potential for bioconcentration in aquatic organisms is low.
GLP:	Not Applicable
Reference:	Hansch, C. et al. (1995). Exploring QSAR. Hydrophobic, Electronic, and Steric Constants, p. 5, Amer. Chem. Soc., Washington, DC, ACS Prof. Ref. Book, Heller SR (consult

ed.) (HSDB/354).

Lyman, W. J. et al. (1990). Handbook of Chemical Property Estimation Methods, pp. 5-4, 5-10, Amer. Chem. Soc., Washington, DC (HSDB/354).

Franke, C. et al (1994). Chemosphere, 29:1501-14 (HSDB/354).

SRC (Syracuse Research Corporation) (n.d.). (HSDB/354).

Reliability: Estimated value based on acceped model.

Additional References for Bioconcentration: None Found.

4.0 Ecotoxicity

4.1 Acute Toxicity to Fish

Type:	**NOEC**
Species:	*Poecilia reticulata* (Guppy)
Value:	> 4000 mg/L
Method:	NEN 6504; semistatic. With respect to rapid volatilization of DME, sealed flasks were used for the testing. Renewal of test solutions occurred after 48 hours.
GLP:	Yes
Test Substance:	Dimethyl ether, purity not specified
Results:	All fishes survived the dosages studied (nominal concentrations of 1900 and 3200 mg/L, maximum concentration of DME measured 4100 g/mL).
Reference:	Akzo sponsored study, March 1988 (cited in IUCLID (1995). IUCLID Data Sheet "dimethyl ether" (October 23)).
Reliability:	Not assignable because limited study information was available.

Additional References for Acute Toxicity to Fish: None Found.

4.2 Acute Toxicity to Invertebrates

Type:	**NOEC**
Species:	*Daphnia magna*
Value:	> 4000 mg/L
Method:	NEN 6501. With respect to rapid volatilization of DME, sealed flasks were used for the testing.
GLP:	Yes
Test Substance:	Dimethyl ether
Results:	All animals survived the dosages studied (nominal

	concentrations of 1000 and 3200 mg/L, maximum concentration of DME measured 4400 g/mL).
Reference:	Akzo sponsored study, March 1988 (cited in IUCLID (1995). IUCLID Data Sheet "dimethyl ether" (October 23)).
Reliability:	Not assignable because limited study information was available.

Additional References for Acute Toxicity to Invertebrates: None Found.

4.3 Acute Toxicity to Aquatic Plants:

Type:	**96-hour EC_{50}**
Species:	Algae
Value:	1099 mg/L ($\log_{10}$ Kow of 0.10)
Method:	Modeled
GLP:	Not Applicable
Test Substance:	Dimethyl ether
Results:	No Data
Reference:	Meylan, W. M. and P. H. Howard (1999). User's Guide for the ECOSAR Class Program, Version 0.993 (Mar 99), prepared for J. Vincent Nabholz and Gordon Cas, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics, Washington, DC, prepared by Syracuse Research Corp., Environmental Science Center, Syracuse, NY 13210 (submitted for publication).
Reliability:	Estimated value based on accepted model.

5.0 Mammalian Toxicity

5.1 Acute Toxicity

Type:	**Oral Toxicity:** No Data.

Type:	**Inhalation 4-hour LC_{50}**
Species/Strain:	Male rats/ChR-CD®
Value:	164,000 ppm (95% confidence limits,142,000 and 203,000 ppm)
Method:	Groups of 10 rats, 7 – 8 weeks old, were exposed to DME gas by whole-body method for single 4-hour periods. Exposure concentrations tested were 84,000, 121,000, 152,000, 169,000, and 205,000 ppm. Food and water were available *ad libitum* at all times other than the exposure. Atmospheres were generated by means of a single-stage regulator through a flow meter directly into the top of a 20-liter glass exposure chamber. Dilution air flowing through a flow meter joined the DME stream at the top of

	the chamber. The air/DME flow was maintained at 10 L/minute. Gas standards and samples were analyzed with a thermal conductivity detector on a gas chromatograph. Chamber atmosphere was sampled at approximately 30-minute intervals. During exposure, observations of clinical signs of toxicity were made. After exposure, the surviving rats were returned to their respective cages and were observed daily (weekends excluded) for 14 days. Body weights and clinical signs were recorded. Surviving rats were sacrificed after a 14-day recovery period. The LC_{50} of DME was calculated via probit analysis.
GLP:	No
Test Substance:	Dimethyl ether, purity 99.9%
Results:	Mortality of 0/10, 3/10, 2/10, 7/10, and 7/10 occurred in the 84,000, 121,000, 152,000, 169,000, and 205,000 ppm groups, respectively. All but one death (205,000 ppm) occurred during the exposures. During exposure, the rats demonstrated ataxia (84,000 ppm and above), unresponsiveness to noise (121,000 ppm and above), anesthesia (84,000 ppm and above), paw waving (84,000 ppm), roving eyeballs (84,000 ppm), and coma (121,000 ppm and above). Ataxia was defined as uncoordinated. Anesthesia was considered unconsciousness with steady respirations (>50/min) and coma was considered unconsciousness with irregular, periodic or slow (<50/min) and shallow respirations. Post-exposure, survivors rapidly awoke and showed no clinical signs, other than transient weight loss for 1-2 days and sporadic lung noise.
Reference:	DuPont Co. (1979). Unpublished Data, Haskell Laboratory Report No. 847-79 (also cited in TSCA fiche OTS0540660). Brittelli, M. R. and L. W. Smith (1981). The Toxicologist, 1:79 (Abstract No. 286).
Reliability:	High because a scientifically defensible or guidelined method was used.

Type:	**Acute Inhalation**
Species/Strain:	Human
Value:	No Data
Method:	Human subjects were exposed to 50,000, 75,000, 82,000, 100,000, 144,000, or 200,000 ppm for approximately 60 minutes. Exposures were terminated if unconsciousness occurred in the subjects. The number of subjects tested in each group was not reported.

	The test substance was prepared by Newth's method and after passing through alcohol, silver nitrate solution, a limetower, and a little strong sulphuric acid, was collected in sulphuric acid and subsequently liberated by the addition of water. After passing through an alkaline solution, it was collected in gas-bags and diluted with air and oxygen to the required concentrations. Clinical symptoms were noted for all concentrations. Effects on reaction times were tested at all dose levels, memory (writing of the Lord's Prayer) was tested at 82,000 and 100,000 ppm, muscular coordination (as exemplified by the act of writing) was observed at 82,000, 100,000, and 144,000 ppm, and typewriting was tested at 100,000 ppm.
GLP:	No
Test Substance:	Dimethyl ether, purity not specified
Results:	In human subjects, 50,000 and 75,000 ppm of DME caused feelings of mild intoxication but no objective symptoms beyond slight lack of attention after 12-minutes exposure to the higher concentration. At 82,000 ppm, some incoordination developed after 21.5 minutes, and a complaint was made of indistinct vision. At 100,000 ppm, no objective symptoms occurred during the first 15 minutes. Distinct signs of incoordination developed after 21 minutes of exposure. The experiment continued for 64 minutes, with the subject unable to do simple tasks (i.e., balancing of the head required special effort, estimation of time was lost, simple multiplication and memory were affected). At 144,000 ppm, symptoms first occurred after 7 minutes with the subject losing consciousness after 26 minutes. Inhalation of 200,000 ppm caused unconsciousness in 17 minutes.
Reference:	Davidson, B. (1925). J. Pharmacol. Exp. Ther., 26:43-48.
Reliability:	Not assignable because limited study information was available.

Additional References for Acute Inhalation Toxicity:

Data from these additional sources support the study results summarized above. The studies were not chosen for detailed summarization because the data were not substantially additive to the database.

Caprino, L. and G. Togna (1975). Eur. J. Toxicol. Environ. Hyg., 8(5):287-290 (CA84:85154k).

Caprino, L. and G. Togna (1975). Eur. J. Toxicol. Environ. Hyg., 8(5):287-290

(CA84:85154k).

Arniot, L. G. (1932). Presse Med., 40:300-302 (CA27:781[9]).

Brown, W. E. (1924). J. Pharmacol. Exp. Ther., 23:485-496.

Type: **Dermal Toxicity:** No Data.

Type: **Dermal Irritation:** No Data.

Additional Reference for Acute Dermal Irritation:

The following source provides information related to dermal effects but does not report effects of a dermal irritation study.

Gosselin, R. E. et al. (1984). Clinical Toxicology of Commercial Products, 5th ed., II-185 (Abstract No. 475).

Type: **Dermal Sensitization:** No Data.

Type: **Eye Irritation:** No Data.

Type: **Cardiac Sensitization**
Species/Strain: Dogs/Beagle
Value: Cardiac sensitizer ≥ 200,000 ppm
Method: Beagle dogs were exposed to 100,000, 200,000, or 300,000 ppm for 5 minutes. There were 6 dogs in the 100,000 and 300,000 ppm groups and 12 dogs in the 200,000 ppm group. The dogs received a control injection of epinephrine (0.008 mg/kg) intravenously, prior to exposure and a challenge injection (same dosage) after breathing the test material for 5 minutes. The desired concentrations (calculated) were achieved by delivering a metered volume of the vapor or gas from the pressured cylinder containing the test substance and diluting it with a known volume of air. The flow meter used for monitoring the test compound had been previously calibrated with the compound by a dry gas test meter.
GLP: No
Test Substance: Dimethyl ether, purity 99.8%
Results: Marked responses were observed in 0/6 (0%), 2/12 (16.7%), and 2/6 (33.3%) dogs administered 100,000, 200,000, or 300,000 ppm DME, respectively. A marked response indicated the development, after the challenge injection of epinephrine, of a cardiac arrhythmia which was considered to pose a serious threat to life. It was concluded that DME

	was capable of sensitizing the mammalian heart to epinephrine.
Reference:	DuPont Co. (1969). Unpublished Data, Haskell Laboratory Report No. 354-69 (also cited in TSCA fiche OTS0514917, OTS0520943, OTS0520982, OTS0520985). Reinhardt, C. F. et al. (1971). Arch. Environ. Health, 22:265-279.
Reliability:	Medium because a suboptimal study design was used where animals were not individually titrated with epinephrine.

Additional Reference for Cardiac Sensitization:

Data from this additional source were not summarized because the study design was not adequate.

Hazleton Labs. Amer. Inc. (1976). TSCA fiche OTS0537125.

5.2 Repeated Dose Toxicity

Type:	**2-Year Inhalation**
Species/Strain:	Rats/Crl:CD®(SD)BR
Sex/Number:	Male and female/100 per group
Exposure Period:	2 years
Frequency of Treatment:	6 hours/day, 5 days/week (excluding holidays)
Exposure Levels:	0, 2000, 10,000, 25,000 ppm
Method:	Groups of 100 male and 100 female rats were exposed to 0, 2000, 10,000, or 25,000 ppm DME for up to 2 years. Food and water were available to the rats *ad libitum* except during exposures. The age of rats was not specified. Rats were exposed whole-body to the vapor. During exposures, chamber temperature and relative humidity were maintained at approximately 23±2°C and 50±10%, respectively. DME vapors were generated by warming the compressed-gas cylinders containing liquefied DME in a 21-27 °C water bath. The vapors were metered into the intake manifold at the top of the exposure chamber. Filtered, conditioned air also entered the top of the chamber, swept the test material into respective exposure chambers, and was exhausted out the bottom of the chambers. Chamber concentrations of DME were regulated by controlling the flow rate of DME vapors into the chamber. Filtered air, alone, was metered in a similar manner into the control chamber. Total flow of air

(control group) or air plus DME was maintained at approximately 800 L/minute. Chamber atmospheres were quantitatively analyzed for DME by gas chromatography.

All rats were weighed and individually handled and carefully examined for abnormal behavior and appearance once weekly during the first 3 months of the study and twice monthly for the remainder of the study. Cage-site examinations to detect moribund or dead rats and abnormal behavior and appearance were conducted at least twice daily throughout the study. Approximately 3, 6, 9, 12, and 18 months after the study's initiation, hematological, clinical chemical, and urine analytical evaluations were conducted on 10 male and 10 female rats randomly selected from each exposure group. Fourteen hematological and 10 clinical chemistry parameters were measured or calculated. On the day prior to each bleeding time, an overnight urine specimen was collected and 9 urine chemistry parameters were measured or calculated. Gross and histopathological evaluations were conducted on 10 rats/sex/exposure group after 6, 12, and 18 months of exposure and on all rats alive after 2 years of exposure. Approximately 50 organs and/or tissues were saved for microscopic examinations. Organ weights were recorded on 10.

GLP: Yes

Test Substance: Dimethyl ether, purity 99.98%

Results: The overall mean weekly chamber concentrations of DME vapors were 2100 ± 200, 10,200 ± 900, and 24,700 ± 1900 ppm for the 2000, 10,000, and 25,000 ppm groups, respectively.

Body weights were greater and survival rates were less than the control group for male rats in the 10,000 and 25,000 ppm DME groups. No clear association could be made between body weight increases and decreased survival even though these changes were concurrent observations in the same exposure groups. No histological lesion was found that could explain the decrease in survival rate. Body weights and survival rate of the female rats were statistically the same as the female rats in the control group.

Increased incidences of stained wet/perineal area were observed in male rats in the groups exposed to DME vapors. Since increases were observed in male rats in all exposure groups and since these increases were not exposure-related, the significance of this finding was not clear. Increased incidences of torn ears were observed in the male and female rats in the 10,000 and 25,000 ppm groups. Ear punching was used to identify the animals in the study. The 25,000 ppm rats had double punching of one ear, and the 10,000 ppm rats had single punching in both ears and this may have led to an increased incidence of torn ears in these groups.

Compound-related hematologic or clinical chemistry effects were not observed for male rats exposed to DME vapors for 2 years. A compound-related hemolytic effect was observed in male rats in the high-exposure group at 6 months on test. This effect was characterized by a decrease in erythrocyte count, increases in spleen weight, histological evidence of splenic congestion, along with normal bone marrow histology. A decrease in erythrocyte count was also observed in female rats at the high-exposure group at 3 months that was considered compound-related. These changes were interpreted to be transient effects that were not representative of the long-term effects of DME.

The incidence of clinically observable masses in female rats was higher in the 2000, 10,000, and 25,000 ppm groups. The masses were primarily ventral (axillary, inguinal, and perineal). An increase in the incidence of mammary tumors (benign or malignant) was observed in female rats in the 25,000 ppm DME group. These incidences of ventral masses and mammary tumors were considered not to be compound related because the incidences of masses and tumors in the control group were uncharacteristically low in comparison with the control groups incidence in studies previously conducted at Haskell Laboratory.

No DME-related histological lesion was consistently observed throughout the study.

The no-observable-effect-level (NOEL) was 2000 ppm DME based on an increase in body weight and a decrease in survival in male rats exposed to 10,000 or 25,000 ppm DME vapors and on hemolytic effects noted in male rats exposed to 25,000 ppm DME vapors for 6 months. No neoplastic lesions were observed that could be attributable to DME exposure. DME was not carcinogenic.

Reference: DuPont Co. (1986). Unpublished Data, Haskell Laboratory Report No. 198-86.

Reliability: High because a scientifically defensible or guidelined method was used.

Additional References for Repeated Dose Toxicity:

Data from these additional sources support the study results summarized above. The studies were not chosen for detailed summarization because the data were not substantially additive to the database.

Collins, C. J. et al. (1978). Toxicology, 11(1):65-71 (CA89:191947j).

DuPont Co. (1980). Unpublished Data, Haskell Laboratory Report No. 583-80 (also cited in Brittelli, M. R. and L. W. Smith (1981). The Toxicologist, 1:79 (Abstract No. 286)).

Reuzel, P. G. J. (1978). CIVO-TNO Report No. 5717 (also cited in Reuzel, P. G. J. et al. (1981). Aerosol Rep., 20(1):23-28).

Reuzel, P. G. J. and R. A. Woutersen (1983). Unpublished CIVO-TNO Report No. 83.263/201323.

Kruysse, A. et al. (1976). CIVO-TNO Report No. R 5004 (cited in IUCLID (1995). IUCLID Data Sheet “dimethyl ether” (October 23)).

Gosselin, R. E. et al. (1984). Clinical Toxicology of Commercial Products, 5th ed., II-185 (Abstract No. 475).

Data from this additional source was not chosen for detailed summarization because the test substance was a mixture or otherwise inappropriate.

Bulgakov, V. V. and D. S. Slobodskoi (1977). Gig. Sanit., 4:22-25 (CA87:34050c).

5.3 Developmental Toxicity

Species/Strain:	Rats/Crl:CD®(SD)BR
Sex/Number:	Female For Part I (14 controls and 7 for DME groups) For Part II (27/group)
Route of Administration:	Inhalation
Exposure Period:	Days 6-15 of gestation, Cesarean section Gestation Day 21
Frequency of Treatment:	6 hours/day
Exposure Levels:	0, 5000, 20,000, 40,000 ppm DME (Part I) 0, 1250, 5000, 20,000 ppm DME (Part II)

Method:

The age of the animals was not specified, however, the rats in Part I weighed between 150 and 160 grams upon arrival and the rats in Part II weighed between 240 and 270 grams. Food and water were available to the rats *ad libitum* except during exposures. The female rats were mated to mature males of the same strain on an as-needed basis. Mating was verified by detection of spermatozoa in the vaginal lavage each morning following overnight cohabitation. Mated females were housed 2/cage in Part I and individually in Part II. Those rats exposed to DME, and those from the control group, were housed in the same room (Part I) or in separate rooms (Part II) after each daily exposure.

For Part I, DME vapors were metered from a stainless steel cylinder, through a flowmeter, and into a dilution air stream prior to entry into the exposure chamber. The mixed atmosphere was introduced into the top of the exposure chamber and vented from the bottom. Chamber atmospheres were quantitatively analyzed for DME by gas chromatography. The exposure chambers were cylindrical glass chambers (12 inches in diameter). Twenty liter chambers were used for the test groups and 40 L chambers for the control group.

For Part II, DME vapors were metered from a stainless steel cylinder, through a flowmeter into a mixing flask. In the mixing flask, the DME was mixed with 10 L/min air stream prior to entry into the exposure chamber. This mixture was introduced into the top of the exposure chamber where it was further diluted with room air to a total flow of 250 L/min. The exposure chambers were 750 L glass and stainless steel chambers.

Body weights and food consumption were measured periodically during gestation. The animals were observed for signs of toxicity and changes in behavior upon arrival, at breeding, and daily from days 6-21 of gestation when the dams were sacrificed. The dams were examined for gross pathologic changes, liver and uterine weights were recorded, and reproductive status was determined. Corpora lutea, implantation sites, live and dead fetuses, resorptions, fetal weight, and the number and position of all live, dead, and resorbed fetuses were recorded. The uterus of each apparently "non-pregnant" rat was stained to detect very early resorptions. All live and dead fetuses were weighed and sexed externally and internally and the live fetuses were examined for external alteration. Approximately one-third of the fetuses were examined for visceral alterations, the heads were removed and underwent a head examination. The above fetuses and all those remaining from each litter were examined for skeletal abnormalities.

GLP: Yes

Test Substance: Dimethyl ether, purity 99.9%

Results: In Part I, the DME concentrations generated in the exposure chambers were 0, 4500 ± 260, 19,500 ± 1170, and 38, 200 ± 4580 ppm for the 0, 5000, 20,000, and 40,000 ppm groups, respectively. In Part II, the DME concentrations generated in the exposure chambers were 0, 1250 ± 50, 5000 ± 230, and 20,000 ± 580 ppm for the 0, 1250, 5000, and 20,000 ppm groups, respectively.

Dams exposed to DME at the 40,000 ppm level showed no response to a sound stimulus during exposure and gained significantly less weight during the early exposure period than did the control dams. In groups exposed to the lower levels, the only DME-related effect demonstrated among the dams was a slight decrease in response to sound at the 20,000 ppm DME level. The response of the 5000 ppm group was equivocal.

Pregnancy ratios for Part I were 14/14, 7/7, 7/7, and 7/7 for the 0, 5000, 20,000, and 40,000 ppm groups, respectively. Pregnancy ratios for Part II were 25/27, 24/27, 27/27, and 25/27 for the 0, 1250, 5000, and 20,000 ppm groups, respectively. A summary of other reproductive outcomes (means/litter) are provided in the tables below:

Part I:

Concentration (ppm):	0	5000	20,000	40,000
Corpora lutea:	15.4	15.9	15.4	16.4
Implantations:	14.9	15.0	15.1	16.0
No. of Resorptions:	1.4	1.0	1.3	1.3
Total No. of Fetuses:	NR	NR	NR	NR
Total No. of Live Fetuses:	189	98	97	103
Mean Fetal Weight (g):	4.0	3.8	3.8	3.6
Sex Ratio:	NR	NR	NR	NR

Part II:

Concentration (ppm):	0	1250	5000	20,000
Corpora lutea:	16.7	16.3	15.2	15.7
Implantations:	14.0	15.3	14.7	14.9
No. of Resorptions:	1.0	1.0	1.0	0.9
Total No. of Fetuses:	NR	NR	NR	NR
Total No. of Live Fetuses:	13.0	14.3	13.7	14.0
Mean Fetal Weight (g):	3.8	3.7	3.8	3.7
Sex Ratio:	NR	NR	NR	NR

NR = Not Reported

DME was not shown to be teratogenic at any level of exposure in this study. Embryo-fetal toxicity was evident at the 20,000 and 40,000 ppm DME levels, which was expressed as decreased fetal body weight (of borderline statistical significance in the 20,000 ppm group) and as an increased incidence of several skeletal variations (partial rib development in the lumbar region and partial or complete doubling of one or more vertebral centra). An increased incidence of one skeletal variation (extra ossification centers in the lumbar area), which was exposure-related, was present in the 5000 ppm DME group. Therefore, the “no-effect” level demonstrated for the conceptus was 1250 ppm DME. The skeletal changes noted were those regarded as being normal variants which signified that the dam was stressed sufficiently to express developmental instability inherent in the species. In comparison to maternal effect levels, DME was not demonstrated to represent a unique hazard to the rat conceptus.

Reference: DuPont Co. (1981). Unpublished Data, Haskell Laboratory Report No. 459-81 (also cited in Koeter (1983). CIVO-TNO Report No. 82.331/2200863).

Reliability: High because a scientifically defensible or guidelined method was used.

Additional Reference for Developmental Toxicity:

Data from this additional source support the study results summarized above. The study was not chosen for detailed summarization because the data were not substantially additive to the database.

Koeter, H. B. W. M. and L. M. Appelman (1981). Unpublished CIVO-TNO Report No. V 81.064/200753/200754 (also cited in TSCA fiche OTS0555244 and in Koeter (1983). CIVO-TNO Report No. 82.331/2200863 (also cited in TSCA fiche OTS0546404).

5.4 Reproductive Toxicity:

Species/Strain:	Rats/Crl:CD®(SD)BR
Sex/Number:	Male and female/100 per group
Route of Administration:	Inhalation
Exposure Period:	2 years
Frequency of Treatment:	6 hours/day, 5 days/week (excluding holidays)
Exposure Levels:	0, 2000, 10,000, 25,000 ppm
Method:	A 2-year inhalation study was conducted in male and female rats (see section 5.2 for details on the study design). Terminal sacrifices occurred at 6, 12, 18, and 24 months. Ten rats/sex/group were sacrificed and necropsied at 6, 12, and 18 months and all rats alive at the 2-year time point. All rats underwent both gross and microscopic examinations. Reproductive organs included in the histopathological evaluation included testis, epididymis, prostate, seminal vesicles, cervix, mammary gland, ovary, uterus, and vagina. The testis was weighed.
GLP:	Yes
Test Substance:	Dimethyl ether, purity 99.98%
Results:	No compound-related effects on the reproductive organs of either male or female rats were observed. An increase in the incidence of mammary tumors (benign or malignant) was observed in female rats in the 25,000 ppm DME group. The incidence of mammary tumors was considered not to be compound related because the incidences of tumors in the control group were uncharacteristically low in comparison with the control groups incidence in studies previously conducted at Haskell Laboratory.
Reference:	DuPont Co. (1986). Unpublished Data, Haskell Laboratory Report No. 198-86.
Reliability:	Medium because a suboptimal study design was used.

Additional References for Reproductive Toxicity: None Found.

5.5 Genetic Toxicity

Type:	***In vitro* Bacterial Reverse Mutation Test**
Tester Strains:	*Salmonella typhimurium* strains TA97a, TA98, TA100 and TA1535 and *Escherichia coli* strain WP2*uvr*A (pKM101).
Exogenous Metabolic Activation:	With and without Aroclor®-induced rat liver S-9
Exposure Concentrations:	Trials 1 and 2: 0, 20, 30, 40, 50,75% Trial 3: 0, 45, 55, 65%
Method:	This study followed the following test guidelines:

U.S. EPA Health Effects Test Guidelines OPPTS 799.9510 (1989)

OECD Guidelines for Testing of Chemicals Section 4: Health Effects, No. 471 (Adopted 1997)

Commission Directive 92/69/EEC, EEC Method B.12

The study consisted of 2 independent trials with and without a metabolic activation system. A third trial, utilizing *S. typhimurium* TA98 with S9 was used to confirm the results. Three replicates were plated for each tester strain, test concentration, and condition. Positive and negative controls were included in all assays. The reaction mixture (S-9 mix) contained glucose 6-phosphate, NADP, NaH_2PO_4, KCL, $MgCL_2$, distilled water, and S-9. Treatments with activation were conducted by adding 0.5 mL of S-9 mix, and 0.1 mL of an overnight culture to 2 mL of top agar. These components were briefly mixed and poured onto a minimal glucose agar plate. Treatments in the absence of the metabolic activation system were identical to those with activation with the exception that 0.5 mL of sterile buffer was used as a replacement for the S-9.

Plates were exposed to dilutions of the test gas in 6-L gas chambers. The test substance and filtered air flows were regulated using individual rotameters, and mixed prior to entry into the chambers. Chambers were placed into an incubator at 37ºC for approximately 48 hours. Gas chromatographic analysis was used to confirm the concentration of test atmospheres.

Bacterial background lawns were evaluated for evidence of test substance toxicity and precipitation. Revertant colonies for a given tester strain and condition were counted by an automated colony counter.

Positive control substances tested in this study included 2-nitrofluorene, N-ethyl-N-nitro-N-nitroguanidine, sodium azide, ICR 191 acridine mutagen, 9,10-dimethyl-1,2-benzanthracene, and 2-aminoanthracene.

Filtered house-line air was the test substance diluent and negative control.

A test substance was classified as positive if the mean number of revertants in any strain (except *S. typhimurium* TA1535) at any concentration was at least 2 times greater than the mean number of revertants of the concurrent negative control, and there was a concentration-related increase in the mean number of revertants per plate in that same strain. For *S. typhimurium* TA1535, there must be no test substance concentration with a mean number of revertants that is at least 3 times greater than the mean number of revertants of its concurrent negative control and a concentration-related increase in the mean number of revertants per plate. A test substance was classified as negative if all positive classification criteria for all strains are not met. Results not meeting criteria for either positive or negative classification were evaluated using scientific judgement and experience and my have been reported as equivacol.

GLP: Yes

Test Substance: Dimethyl ether, purity 99.8%

Results: Negative

Remarks: In trial 1, there was an apparent chamber leakage in one chamber at the high dose without S-9. The other chamber concentrations decreased approximately 50% from the mean at 0-hr and 48-hr. Test substance-related toxicity, as evidenced by a concentration dependent reduction in mean revertant colonies per plate, was observed in all tester strains except *S. typhimurium* strains TA100 and TA1535 without S-9. No evidence of mutagenicity was observed.

In trial 2, test substance-related toxicity was observed in all tester strains in the presence and absence of the metabolic activation system. The chamber concentrations decreased approximately 36% after 48 hours. No mutagenicity was observed with the exception of an equivacol response in *S. typhimurium* strain TA98 in the presence of S-9. At the

50% target concentration, a doubling of mean revertant plate count was observed compared to the mean of the concurrent negative control. There was no concentration-related increase in the tester strain, therefore, the data were considered inconclusive, and a third trial was initiated.

In trial 3, a mean decrease in chamber concentration of approximately 22% was observed with no apparent chamber leakage. Since this trial was negative with evidence of toxicity, the conclusion from trials 2 and 3 is that no evidence of mutagenicity was affirmed.

All acceptability criteria were met in this test. All tester strains exhibited appropriate phenotypic characteristics. No test substance-related precipitate was observed. The mean number of revertants in the negative control for each strain was within the prescribed acceptable historical control range. Mean positive control values for the tester strains exhibited 3-fold increase over the means of the respective negative controls fore each test strain. Differences between targeted and actual doses in both analyses were acceptable for the purposes of this assay and in no way impacted the integrity or validity of this study.

Reference: DuPont Co. (2000). Unpublished Data, Haskell Laboratory Report No. DuPont-4033.

Reliability: High because a scientifically defensible or guidelined method was used.

Additional References for *In vitro* Bacterial Reverse Mutation Assays:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

Bohnenn, L. J. M. (1979). Parfvem. Kosmet., 60(6):209-211.

DuPont Co. (1979). Unpublished Data, Haskell Laboratory Report No. 801-79.

Kramers et al. (1981). RIV-Report No. 627909001 (cited in IUCLID (1995). IUCLID Data Sheet “dimethyl ether” (October 23)).

Williems, M. I. (1978). CIVO-TNO Report No. 5293 (cited in IUCLID (1995). IUCLID Data Sheet “dimethyl ether” (October 23)).

Type: ***In vitro* Chromosome Aberration Test**

Cell type: Human lymphocytes

Exogenous Metabolic Activation:	With and without Aroclor®-induced rat liver S-9
Exposure Concentrations:	Test 1 (3-hour exposure with and without S-9): 0, 35, 50, 70% Test 2 (3-hour exposure with S-9): 0, 35, 50, 70% Test 2 (19-hour exposure without S-9): 0, 20, 35, 50%
Method:	This study followed the following test guidelines:

U.S. EPA Health Effects Test Guidelines OPPTS 870.5375 (1998)

OECD Guidelines for Testing of Chemicals Section 4: Health Effects, No. 473 (Adopted 1997)

Human lymphocytes, in whole blood culture, were stimulated to divide by addition of phytohaemagglutinin, and duplicate cultures were exposed to the test substance. Treatment atmospheres of the test substance were prepared in sterile glass bottles with septum caps. Negative and positive control cultures were also prepared. Mitomycin C and cyclophosphamide were used as positive control substances. Air was used as the negative control substance.

The test substance was sampled from the cylinder into a gas-sampling bag. Air was withdrawn from each pre-warmed (37°C) bottle and then an appropriate volume of test substance gas was introduced from the sampling bag, inserted through the septum cap, and the atmosphere was equilibrated at 37°C. After injection of the lymphocyte culture, air was allowed to enter each bottle through a hollow needle to produce the required concentration at atmospheric pressure. After approximately 48 hours, the cultures in duplicate were injected into the sterile glass bottles. The culture bottles were incubated on their sides at 37°C in a roller apparatus which rotated the bottles once every 8 minutes.

Test 1 included a 3-hour treatment with and without S-9 mix and 16 hours of recovery. Test 2 included a 3-hour treatment with S-9 mix and 16 hours of recovery. Test 2 also included a 19-hour continuous treatment without S-9.

Two hours before the end of the incubation period, cell division was arrested using Colcemid®, the cells harvested and slides prepared, so that metaphase cells could be examined for numerical (polyploidy) and structural chromosomal damage.

In order to assess the toxicity to cultured lymphocytes, the mitotic index was calculated for all cultures treated with the test substance and the negative control. The highest dose level scored for chromosomal damage was, whenever possible, selected as the dose level causing a relative depression in mitotic index of at least 50%.

The test substance was considered to cause a positive response if the following conditions are met:

Statistically significant increases ($p<0.01$) in the frequency of metaphases with aberrant chromosomes (excluding gaps) are observed at one or more test concentration.

The increases exceed the negative control range of this laboratory, taken at the 99% confidence limit.

The increases are reproducible between replicate cultures.

The increases are not associated with large changes in osmolality of the treatment medium or extreme toxicity.

Evidence of a dose-relationship is considered to support the conclusion.

A negative response was claimed if no statistically significant increases in the number of aberrant cells above concurrent control frequencies were observed, at any dose level.

GLP: Yes

Test Substance: Dimethyl ether, purity 100%

Results: Negative

Remarks: A relative depression in mitotic index of at least 50% was observed only at the top two dose levels after the 19-hour exposure in the absence of S-9 mix. The relative mitotic index was 44% and 18% at the test substance dose levels of 50 % and 70 %, respectively. The 50% dose level was selected as the top dose for chromosomal aberration analyses.

In both the absence and presence of S-9 mix, the test substance caused no statistically significant increase in the proportion of metaphase figures containing chromosomal aberrations, at any dose level, when compared with the negative control, in either test.

	No increases in the proportion of polyploid cells were seen in the first test with 3-hour exposure in the absence of S-9 mix. However, in the presence of S-9 mix, a small statistically significant increase in the proportion of polyploid cells was seen at the highest level. In the second test both in the absence (19-hour exposure) and presence (3-hour exposure) of S-9 mix, the test substance caused small statistically significant increases in the proportion of polyploid metaphases at the highest level analyzed. This may indicate that the test substance has the potential to inhibit mitotic processes and to induce numerical chromosome aberrations. All positive control compounds caused large, statistically significant increases in the proportion of aberrant cells, demonstrating the sensitivity of the test system and the efficacy of the S-9 mix.
Reference:	DuPont Co. (2000). Unpublished Data, Haskell Laboratory Report No. DuPont-4110.
Reliability:	High because a scientifically defensible or guidelined method was used.

Additional Reference for *In vitro* Clastogenicity Studies:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

Kramers et al. (1981). RIV-Report No. 627909001 (cited in IUCLID (1995). IUCLID Data Sheet “dimethyl ether” (October 23)).

Type:	***In vivo* Sex-linked Recessive Lethal Assay**
Species/Strain:	*Drosophila melangaster*/Strain not specified
Sex/Number:	Male/No. not specified
Route of Administration:	Inhalation
Exposure Concentrations:	8,000 and 28,000 ppm/ 28,000 ppm
Exposure Duration:	3 days/ 14 days
Method:	No Data
GLP:	No Data
Test Substance:	DME
Results:	Negative
Remarks:	Progeny examination led to the conclusion that DME is not mutagenic under the test conditions.
Reference:	Kramers et al. (1981). Examination of the Genotoxicity of

	DME in short-term studies, RIV-Report No. 627909001 (cited in IUCLID (1995). IUCLID Data Sheet "dimethyl ether" (October 23)).
Reliability:	Not assignable because limited study information was available.

Additional References for *In Vivo* Studies: None Found.